The ABCD Debate

How not to debate!

This house believes that the current NICE guidelines are out of date, lack patient focus, and are not fit for purpose

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SIGN 116 REVIEW AND SET GLYCAEMIC TARGET: HbA1c < 7% (53 mmol/mol) OR INDIVIDUALISED AS AGREED

1st LINE OPTIONS in addition to lifestyle measures; START ONE OF

Metformin (MF)	**Sulphonylurea* (SU)** •If intolerant of metformin •If weight loss/osmotic symptoms

Review and if not reaching target move to 2nd line

Usual approach
Alternative approach **Special considerations**

* Continue medication if EITHER individualised target achieved OR HbA1c falls > 0.5% in 3-6 months

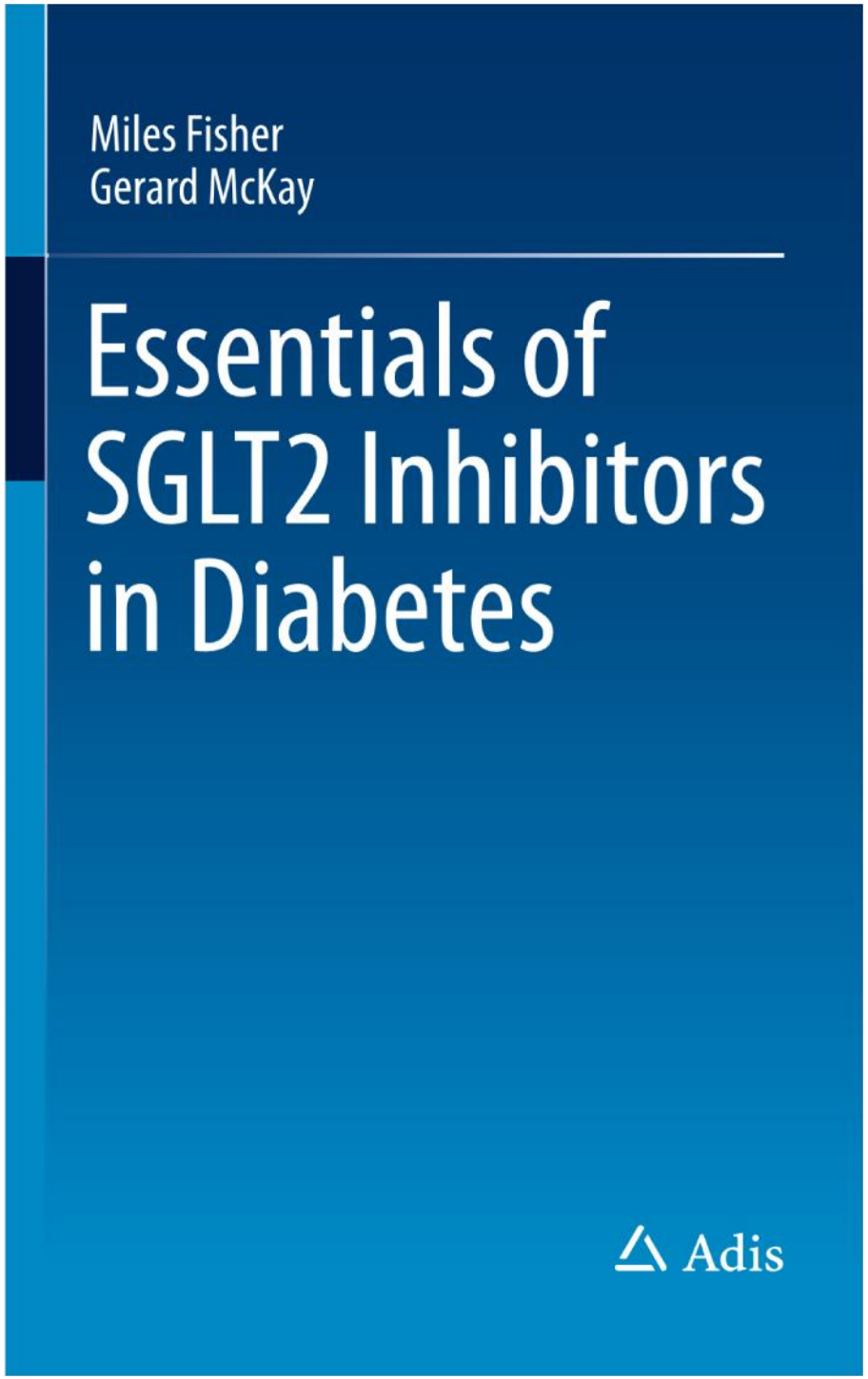
2nd LINE OPTIONS in addition to lifestyle measures, adherence to medication and dose optimisation; ADD ONE OF

Sulphonylurea* (SU)	**Thiazolidinedione*** •If hypos a concern (eg driving, occupational hazards, at risk of falls) and •If no congestive heart failure	**DPP-IV inhibitor*** •If hypos a concern (eg driving, occupational hazards, at risk of falls) •If weight gain a concern

Review and if not reaching target move to 3rd line

3rd LINE OPTIONS in addition to lifestyle measures, adherence to medication and dose optimisation; ADD OR SUBSTITUTE WITH ONE OF

ORAL (continue MF/SU if tolerated)		**INJECTABLE** (if willing to self inject; continue MF/SU if tolerated)	
Thiazolidinedione* If no congestive heart failure	**DPP-IV inhibitor*** If weight gain a concern	**Insulin* (inject before bed)** •If osmotic symptoms/rising HbA1c; NPH insulin initially •If hypos a concern, use basal analogue insulin as an alternative •Add prandial insulin with time if required	**GLP-1 agonists*** •If BMI >30 kg/m^2 •If a desire to lose weight •Usually < 10 years from diagnosis


Miles Fisher
Gerard McKay
Essentials of SGLT2 Inhibitors in Diabetes
Adis

Seven major classes of antidiabetes drugs

Older

- Metformin
- SUs / glitinides
- Glitazones
- Insulin

Newer

- DPP-4 inhibitors
  ="gliptins"
- GLP-1 receptor agonists
  ="tides"
- SGLT-2 inhibitors
  ="flozins"

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

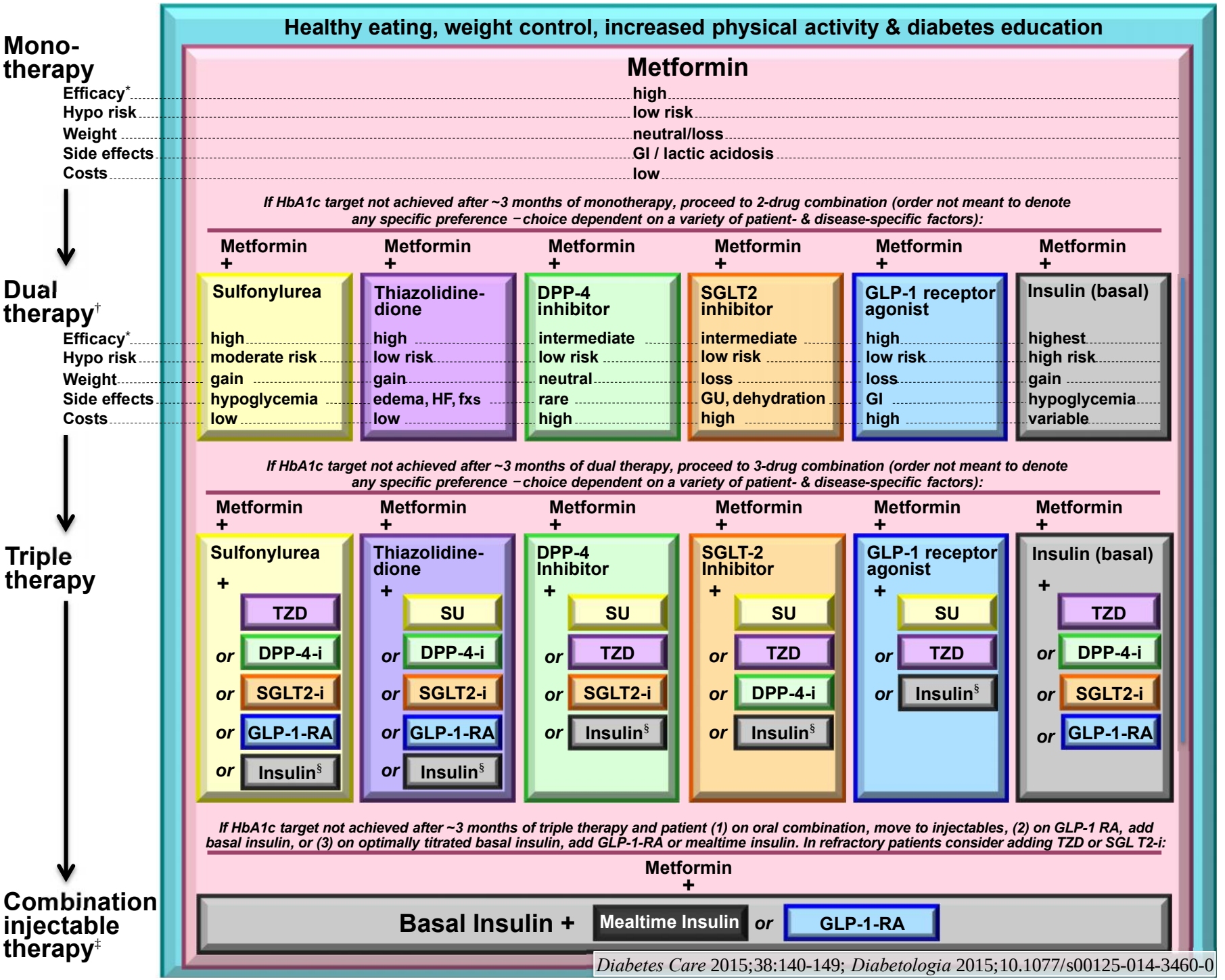
What do we need guidance on?

- In which patients should we avoid the older drugs?
- In which patients should we positively use the new drugs?
- Are there differences in efficacy or safety among the new drug classes?
- Are there differences in efficacy or safety within the new drug classes?

Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

Update **to a Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)**

Diabetes Care 2015;38:140–149
Diabetologia 2015;10.1077/s00125-014-3460-0



Diabetes Care 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0

AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

2016

TASK FORCE

Alan J. Garber, MD, PhD, FACE, *Chair*

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Joshua I. Barzilay, MD, FACE
Lawrence Blonde, MD, FACP, FACE
Zachary T. Bloomgarden, MD, MACE
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Paul D. Rosenblit, MD, PhD, FNLA, FACE
Guillermo Umpierrez, MD, FACP, FACE

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ! Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ! TZD
- ! Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

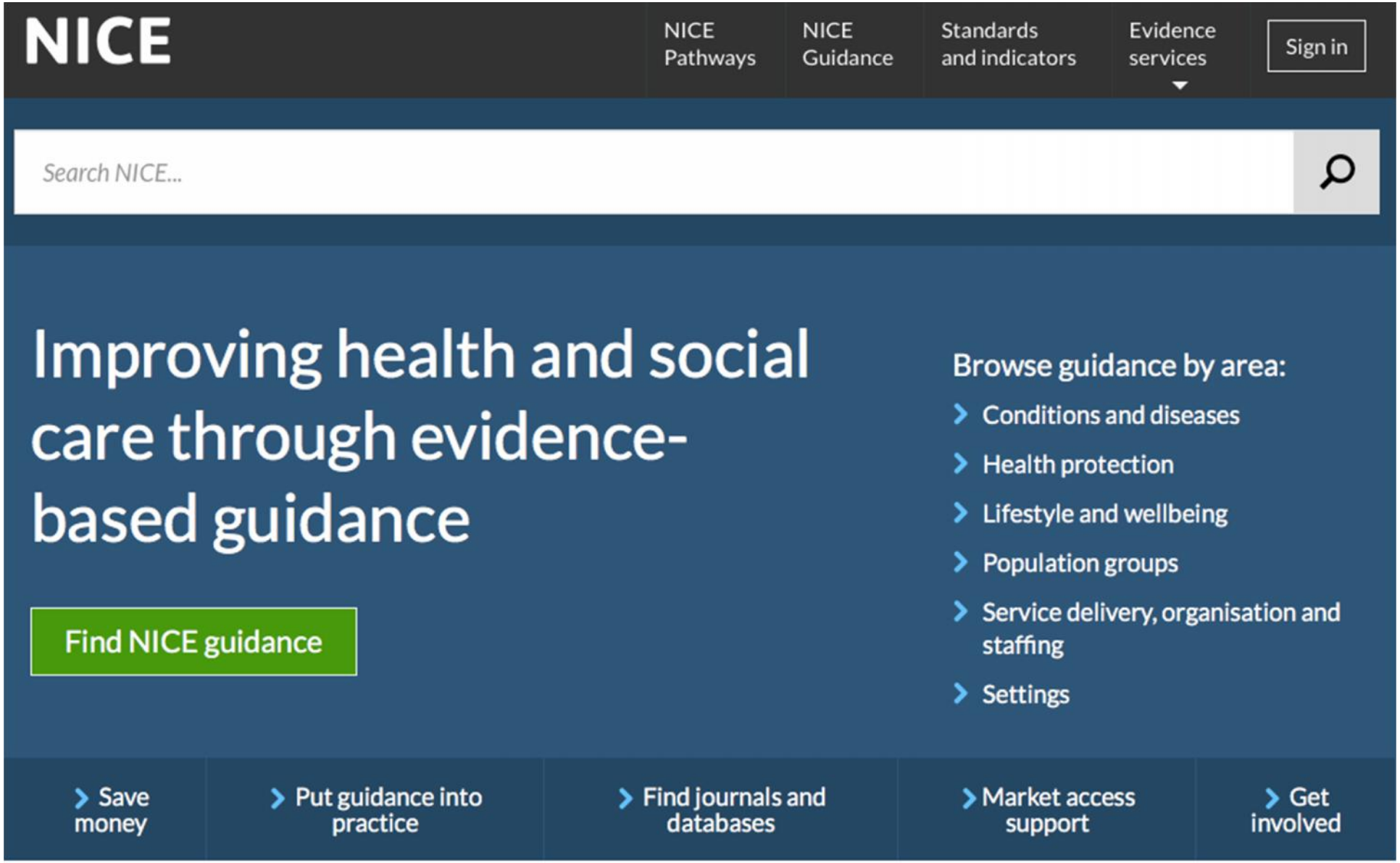
Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ! Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE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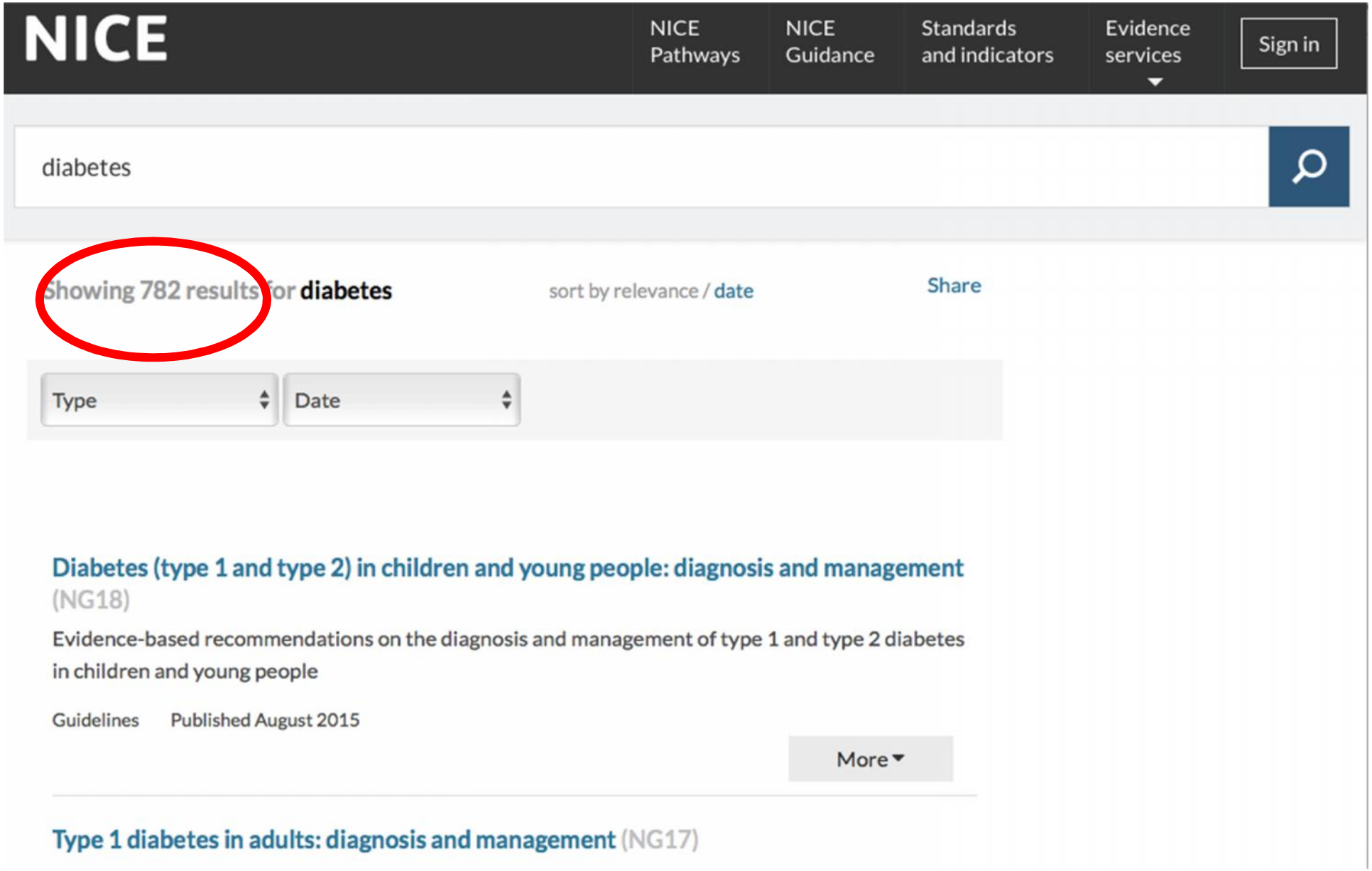
NICE
NICE Pathways
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diabetes
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Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NG18)
Evidence-based recommendations on the diagnosis and management of type 1 and type 2 diabetes in children and young people
Guidelines
Published August 2015
More
Type 1 diabetes in adults: diagnosis and management (NG17)

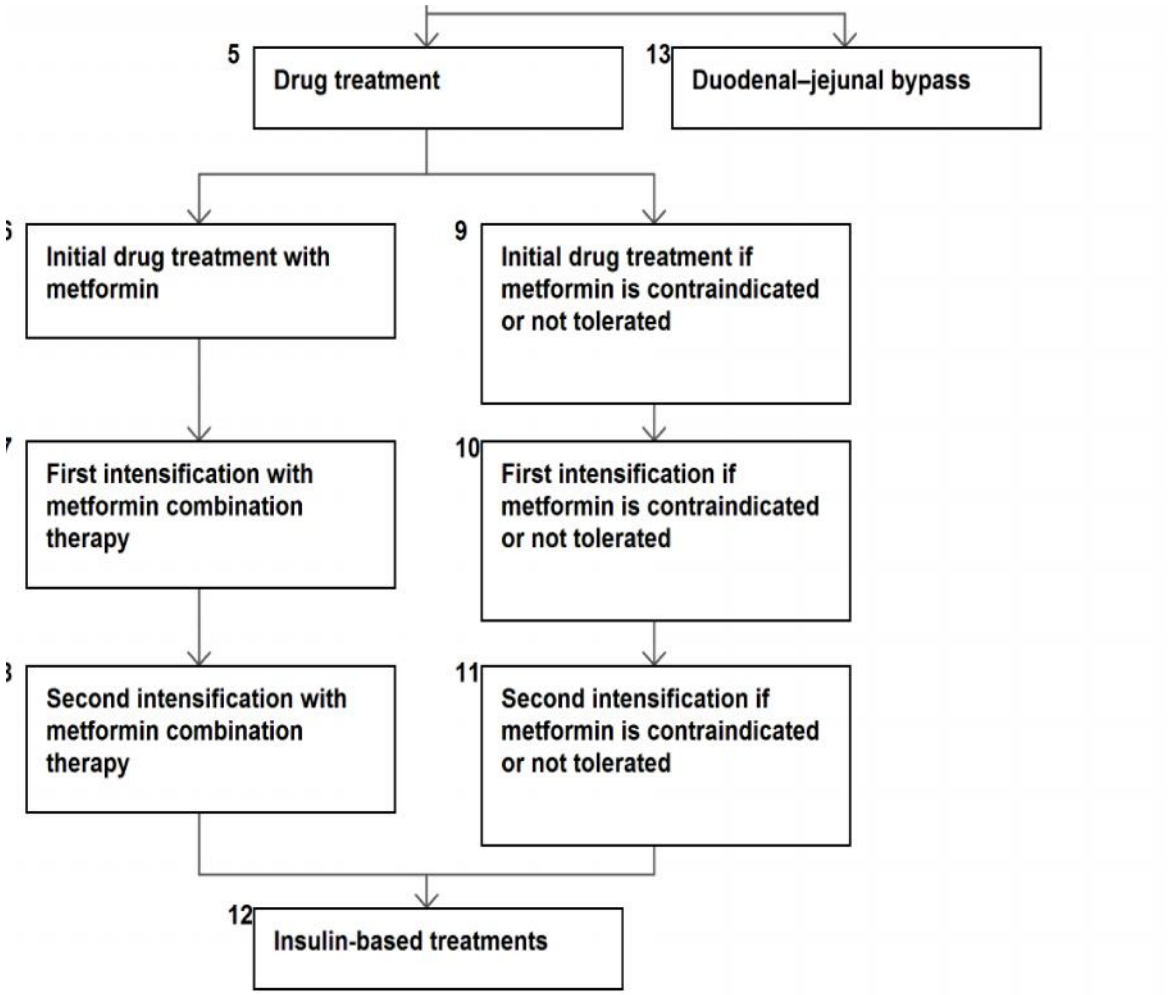
Type 2 diabetes in adults: management (NG28)

Evidence-based recommendations on the care and management of type 2 diabetes in adults

Guidelines Published December 2015 Last updated July 2016

More ▲

Managing blood glucose NICE Pathway



Managing blood glucose NICE Pathway

5 Drug treatment

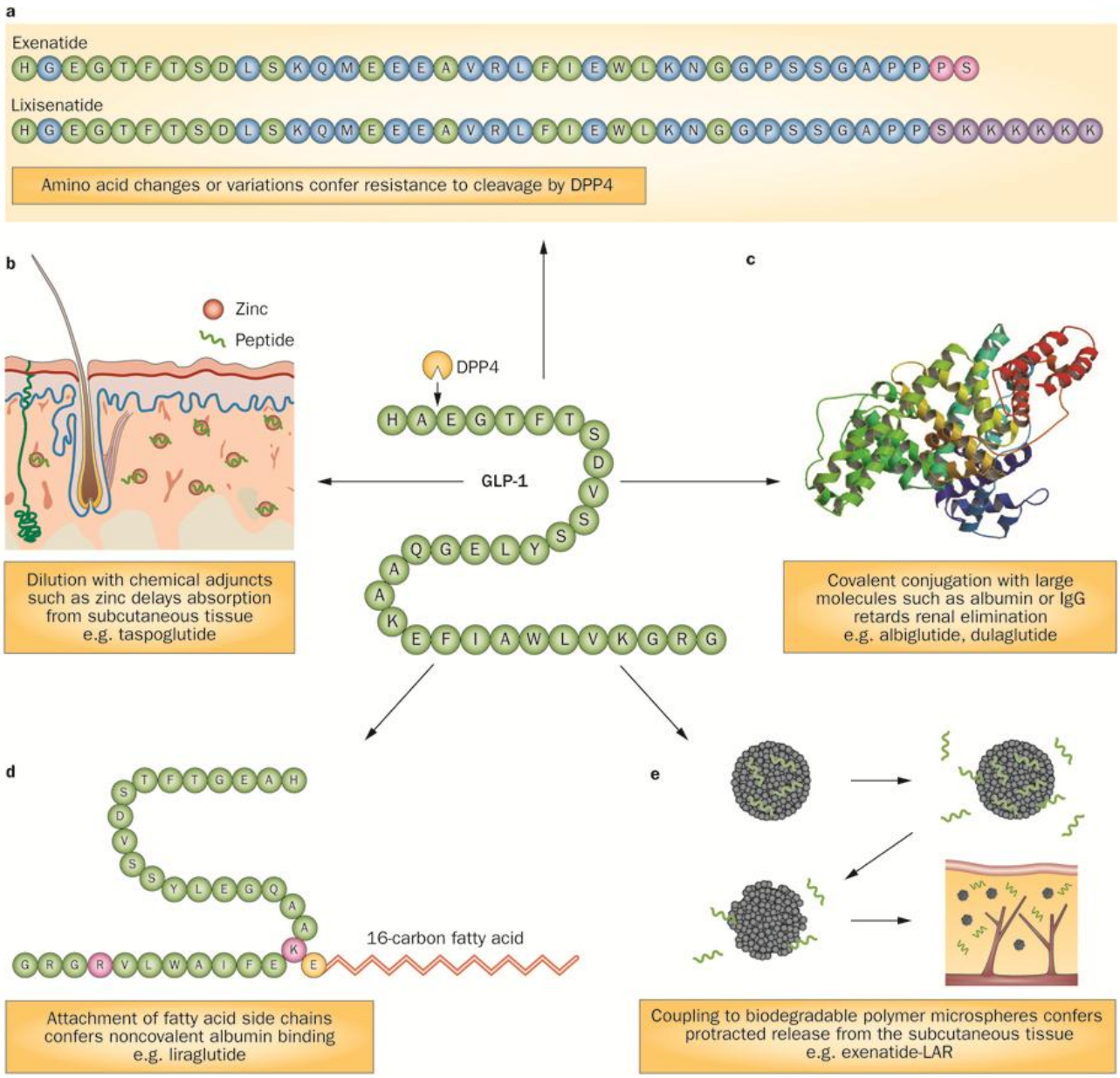
Recommendations in this pathway that cover DPP-4 inhibitors, GLP-1 mimetics and sulfonylureas refer to each of these groups of drugs at a class level.

The NICE guideline has an algorithm for blood glucose lowering therapy in adults with type 2 diabetes.

Are all DPP-4 inhibitors the same?

Drug	Features	Prescribing considerations
Sitagliptin	Once daily, renal excretion	Dose reduction in CKD
Vildagliptin	Twice daily, renal excretion, liver upset described	Dose reduction in CKD, LFT monitoring recommended
Saxagliptin	Once daily, renal excretion	Dose reduction in CKD
Linagliptin	Once daily, biliary excretion	No dose reduction in CKD
Alogliptin	Once daily, renal excretion	Dose reduction in CKD

Are all GLP-1 RAs the same?



Are all GLP-1 RAs the same?

Drug	Frequency of injection	Prescribing considerations
Exenatide	Twice daily Once weekly	Both less effective than liragutide in reducing HbA1c
Liraglutide	Once daily	Most effective in reducing HbA1c & weight
Lixisenatide	Once daily	Less effective than twice daily exenatide and liraglutide in reducing HbA1c
Albiglutide	Once weekly	Less effective than liraglutide in reducing HbA1c & weight
Dulaglutide	Once weekly	Less effective than liragutide in reducing weight

Algorithm for blood glucose lowering therapy in adults with type 2 diabetes

NICE National Institute for Health and Care Excellence

- Reinforce advice on diet, lifestyle and adherence to drug treatment.
- Agree an individualised HbA1c target based on: the person's needs and circumstances including preferences, comorbidities, risks from polypharmacy and tight blood glucose control and ability to achieve longer-term risk-reduction benefits. Where appropriate, support the person to aim for the HbA1c levels in the algorithm. Measure HbA1c levels at 3/6 monthly intervals, as appropriate. If the person achieves an HbA1c target lower than target with no hypoglycaemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA1c level.
- Base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, the person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
- Do not routinely offer self-monitoring of blood glucose levels unless the person is on insulin, on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery, is pregnant or planning to become pregnant or if there is evidence of hypoglycaemic episodes.

If the person is symptomatically hyperglycaemic, consider insulin or an SU. Review treatment when blood glucose control has been achieved.

ADULT WITH TYPE 2 DIABETES WHO CAN TAKE METFORMIN

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:
- Offer standard–release metformin
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%)

If standard-release metformin is not tolerated, consider a trial of modified–release metformin

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider dual therapy with:
  - metformin and a DPP-4i
  - metformin and pioglitazone[a]
  - metformin and an SU
  - metformin and an SGLT-2i[b]
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider:
  - triple therapy with:
    - metformin, a DPP-4i and an SU
    - metformin, pioglitazone[a] and an SU
    - metformin, pioglitazone[a] or an SU, and an SGLT-2i[b]
  - insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

If triple therapy is not effective, not tolerated or contraindicated, consider combination therapy with metformin, an SU and a GLP-1 mimetic[c] for adults with type 2 diabetes who:
- have a BMI of 35 kg/m^2 or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) **and** specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m^2, **and** for whom insulin therapy would have significant occupational implications, **or** weight loss would benefit other significant obesity-related comorbidities

METFORMIN CONTRAINDICATED OR NOT TOLERATED

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:
- Consider one of the following[d]:
  - a DPP-4i, pioglitazone[a] or an SU
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%) for people on a DPP-4i or pioglitazone **or** 53 mmol/mol (7.0%) for people on an SU

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider dual therapy[e] with:
  - a DPP-4i and pioglitazone[a]
  - a DPP-4i and an SU
  - pioglitazone[a] and an SU
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

Insulin-based treatment

- When starting insulin, use a structured programme and continue metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies[f].
- Offer NPH insulin once or twice daily according to need.
- Consider starting both NPH and short-acting insulin either separately or as pre-mixed (biphasic) human insulin (particularly if HbA1c is 75 mmol/mol (9.0%) or higher).
- Consider, as an alternative to NPH insulin, using insulin detemir or glargine[g] if the person: needs assistance to inject insulin, lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes **or** would otherwise need twice-daily NPH insulin in combination with oral blood glucose lowering drugs.
- Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if: the person prefers injecting insulin immediately before a meal, hypoglycaemia is a problem **or** blood glucose levels rise markedly after meals.
- Only offer a GLP-1 mimetic[c] in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team[h].
- Monitor people on insulin for the need to change the regimen.
- An SGLT-2i in combination with insulin with or without other antidiabetic drugs is an option[b]

Abbreviations: [DPP-4i]Dipeptidyl peptidase-4 inhibitor, [GLP-1]Glucagon-like peptide-1, [SGLT-2i]Sodium–glucose cotransporter 2 inhibitors, [SU]Sulfonylurea. Recommendations that cover DPP-4 inhibitors, GLP 1 mimetics and sulfonylureas refer to these groups of drugs at a class level.

a. When prescribing pioglitazone, exercise particular caution if the person is at high risk of the adverse effects of the drug. Pioglitazone is associated with an increased risk of heart failure, bladder cancer and bone fracture. Known risk factors for these conditions, including increased age, should be carefully evaluated before treatment: see the manufacturers' summaries of product characteristics for details. Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2011) advises that 'prescribers should review the safety and efficacy of pioglitazone in individuals after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated'.

b. Treatment with combinations of drugs including sodium–glucose cotransporter 2 inhibitors may be appropriate for some people at first and second intensification; see NICE technology appraisal guidance 288, 315 and 336 on dapagliflozin, canagliflozin and empagliflozin respectively. All three SGLT-2 inhibitors are recommended as options in dual therapy regimens with metformin under certain conditions. All three are also recommended as options in combination with insulin. At the time of publication, only canagliflozin and empagliflozin are recommended as options in triple therapy regimens. The role of dapagliflozin in triple therapy will be reassessed by NICE in a partial update of TA288. Serious and life-threatening cases of diabetic ketoacidosis have been reported in people taking SGLT-2 inhibitors (canagliflozin, dapagliflozin or empagliflozin) or shortly after stopping the SGLT-2 inhibitor. MHRA guidance (2015) advises testing for raised ketones in people with symptoms of diabetic ketoacidosis, even if plasma glucose levels are near normal.

c. Only continue GLP-1 mimetic therapy if the person has a beneficial metabolic response (a reduction of HbA1c by at least 11 mmol/mol [1.0%] **and** a weight loss of at least 3% of initial body weight in 6 months).

d. Be aware that, if metformin is contraindicated or not tolerated, repaglinide is both clinically effective and cost effective in adults with type 2 diabetes. However, discuss with any person for whom repaglinide is being considered, that there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification.

e. Be aware that the drugs in dual therapy should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug.

f. MHRA guidance (2011) notes that cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. It advises that if the combination is used, people should be observed for signs and symptoms of heart failure, weight gain, and oedema. Pioglitazone should be discontinued if any deterioration in cardiac status occurs.

g. The recommendations in this guideline also apply to any current and future biosimilar product(s) of insulin glargine that have an appropriate Marketing Authorisation that allows the use of the biosimilar(s) in the same indication.

h. A consultant-led multidisciplinary team may include a wide range of staff based in primary, secondary and community care.

NICE National Institute for Health and Care Excellence

Algorithm for blood glucose lowering therapy in adults with type 2 diabetes

Patient centred care

- Reinforce advice on diet, lifestyle and adherence to drug treatment.
- Agree an individualised HbA1c target based on: the person's needs and circumstances including preferences, comorbidities, risks from polypharmacy and tight blood glucose control and ability to achieve longer-term risk-reduction benefits. Where app[illegible] the HbA1c level in the algorithm. Measure HbA1c levels at 3/6 monthly intervals, as appropriate. If the person achieves an HbA1c target lower than target with no hyp[illegible] pos[illegible]ble [illegible] fo[illegible]w HbA1c level.
- Base choice of drug treatment on: effectivenes[illegible] safe[illegible] pr[illegible]ences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
- Do not routinely offer self-monitoring of blood glucose levels unless the person is on insulin, on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery, is pregnant or planning to become pregnant or if there is evidence of hypoglycaemic episodes.

If the person is symptomatically hyperglycaemic, consider insulin or an SU. Review treatment when blood glucose control has been achieved.

ADULT WITH TYPE 2 DIABETES WHO CAN TAKE METFORMIN

90%

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:
- Offer standard–release metformin
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%)

If standard-release metformin is not tolerated, consider a trial of modified–release metformin

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider dual therapy with:
  - metformin and a DPP-4i
  - metformin and pioglitazone[a]
  - metformin and an SU
  - [illegible]
- Support the person to ai[illegible]vel of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider:
  - triple therapy with:
    - metformin, a DPP-4i and an SU
    - metformin, pioglitazone[a] and an SU
    - [illegible]
  - insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

If triple therapy is not effective, not tolerated or contraindicated, consider combination therapy with metformin, an SU and a GLP-1 mimetic[c] for adults with type 2 diabetes who:
- have a BMI of 35 kg/m^2 or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) **and** specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m^2, **and** for whom insulin therapy would have significant occupational implications, **or** weight loss would benefit other significant obesity-related comorbidities

METFORMIN CONTRAINDICATED OR NOT TOLERATED

10%

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:
- Consider one of the following[d]:
  - a DPP-4i, pioglitazone[a] or an SU
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%) for people on a DPP-4i or pioglitazone **or** 53 mmol/mol (7.0%) for people on an SU

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider du[illegible]
  - a DPP-4i an[illegible]
  - a DPP-4i a[illegible]
  - pioglitazone[a] and an SU
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

Insulin-based treatment

Insulin

- When starting insulin, use a structured programme and continue metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies[f].
- Offer NPH insulin once or twice daily according to need.
- Consider starting both NPH and short-acting insulin either separately or as pre-mixed (biphasic) human insulin (particularly if HbA1c is 75 mmol/mol (9.0%) or higher).
- Consider, as an alternative to NPH insulin, using insulin detemir or glargine[g] if the person: needs assistance to inject insulin, lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes **or** would otherwise need twice-daily NPH insulin in combination with oral blood glucose lowering drugs.
- Consider [illegible]re-mixed (biphasic) [illegible]reparations that include sh[illegible]ther than pre-mixe[illegible]lude short-acting hu[illegible] the person prefers injecting insulin immediately before a meal, hypoglycaemia is a problem **or** blood glucose levels rise markedly after meals.
- Only offer a GLP-1 mimetic[c] in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team[h].
- Monitor people on insulin for the need to change the regimen.
- [illegible]

The small print

Abbreviations: DPP-4i Dipeptidyl peptidase-4 inhibitor, GLP-1 Glucagon-like peptide-1, SGLT-2i Sodium–glucose cotransporter 2 inhibitors, SU Sulfonylurea. Recommendations that cover DPP-4 inhibitors, GLP 1 mimetics and sulfonylureas refer to these groups of drugs at a class level.

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b. Treatment with combinations of drugs including sodium–glucose cotransporter 2 inhibitors may be appropriate for some people at first and second intensification; see NICE technology appraisal guidance 288, 315 and 336 on dapagliflozin, canagliflozin and empagliflozin respectively. All three SGLT-2 inhibitors are recommended as options in dual therapy regimens with metformin under certain conditions. All three are also recommended as options in combination with insulin. At the time of publication, only canagliflozin and empagliflozin are recommended as options in triple therapy regimens. The role of dapagliflozin in triple therapy will be reassessed by NICE in a partial update of TA288. Serious and life-threatening cases of diabetic ketoacidosis have [illegible]ported in people taking SGLT-2 inhibit[illegible] canagliflozin, dap[illegible]gliflozin or empagliflozin) or shortly after stopping the SGLT-2 inhibitor. MHRA guidance (2015) advises testing for raised ketones in people with symptoms of diab[illegible]

c. Only continue GLP-1 mimetic therapy if the person has a beneficial me[illegible] [illegible]weight loss of at least 3% of initial body weight in 6 months).

d. Be aware that, if metformin is contraindicated or not tolerated, repaglini[illegible] However, discuss with any person for whom repaglinide is being considered, that there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification.

e. Be aware that the drugs in dual therapy should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug.

f. MHRA guidance (2011) notes that cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. It advises that if the combination is used, people should be observed for signs and symptoms of heart failure, weight gain, and oedema. Pioglitazone should be discontinued if any deterioration in cardiac status occurs.

g. The recommendations in this guideline also apply to any current and future biosimilar product(s) of insulin glargine that have an appropriate Marketing Authorisation that allows the use of the biosimilar(s) in the same indication.

h. A consultant-led multidisciplinary team may include a wide range of staff based in primary, secondary and community care.

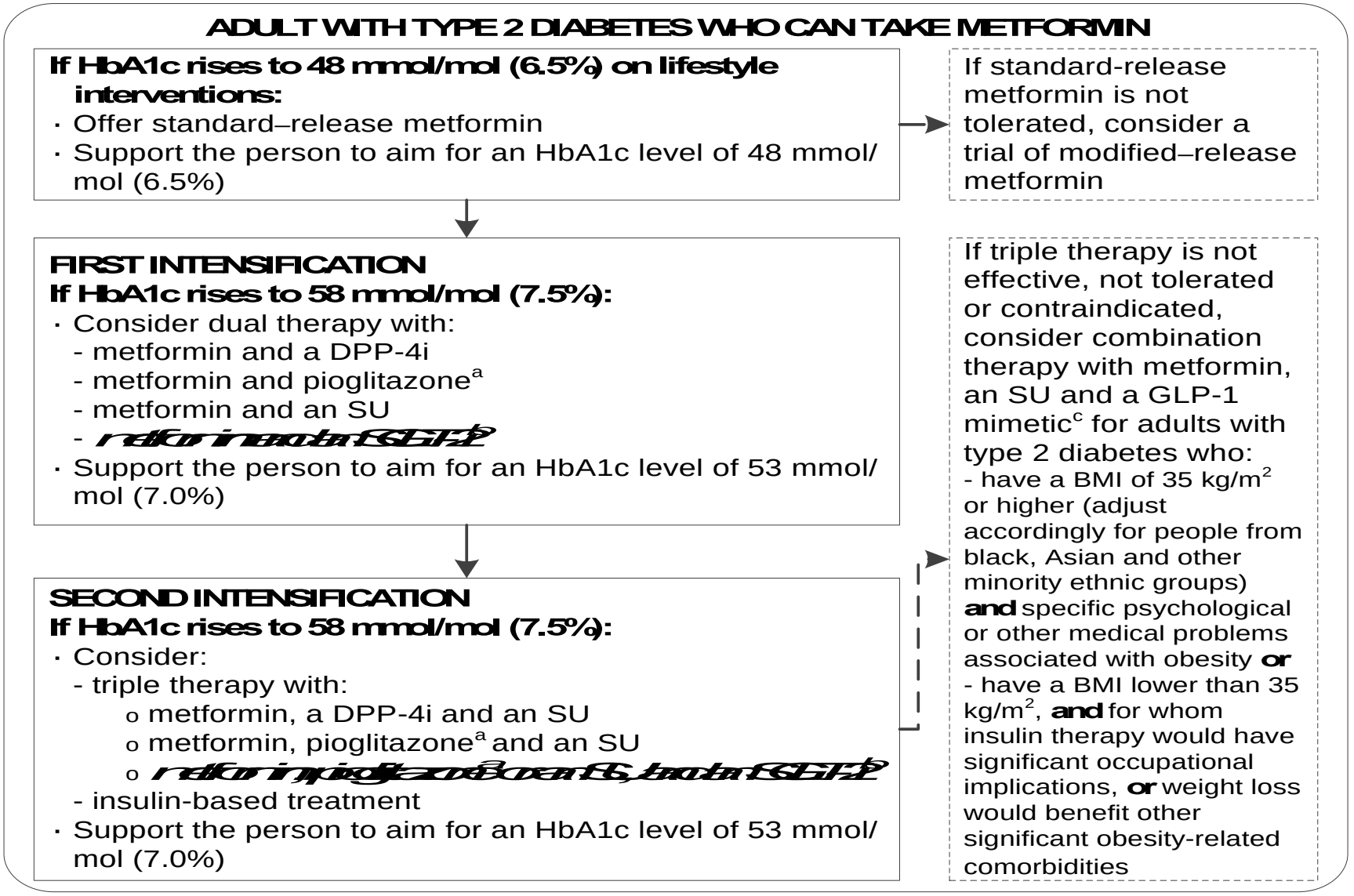
1. Patient-Centered Approach

"...providing care that is respectful of and responsive to individual patient preferences, needs, and values - ensuring that patient values guide all clinical decisions."

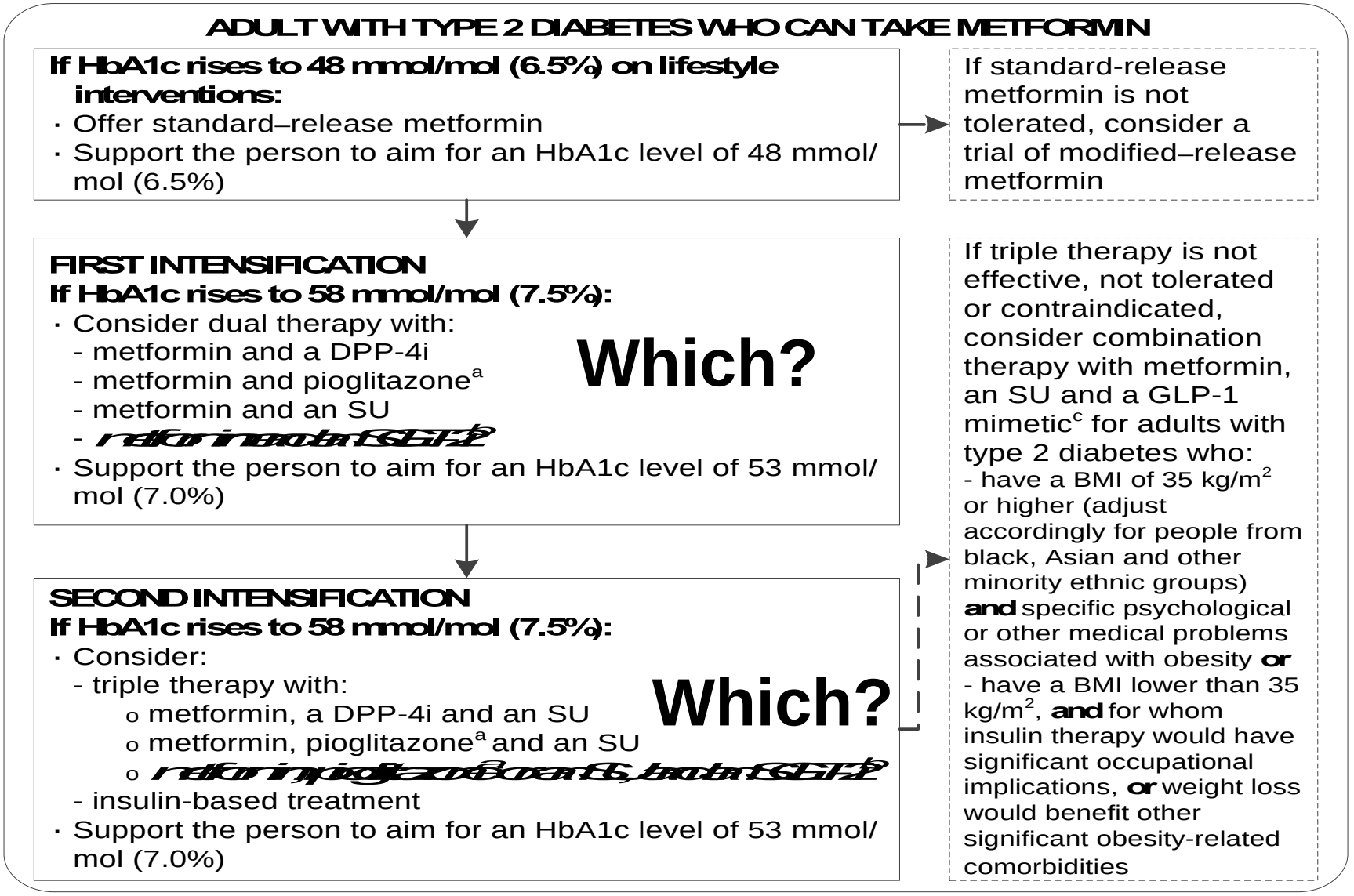
- Gauge patient's preferred level of involvement.
- Explore, where possible, therapeutic choices. Consider using decision aids.
- Shared Decision Making – a collaborative process between patient and clinician, using best available evidence and taking into account the patient's preferences and values
- Final decisions regarding lifestyle choices ultimately lie with the patient.

Diabetes Care 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596

For the 90% who can take metformin



For the 90% who can take metformin



Why so late?

Effects of Exenatide (Exendin-4) on Glycemic Control Over 30 Weeks in Patients With Type 2 Diabetes Treated With Metformin and a Sulfonylurea

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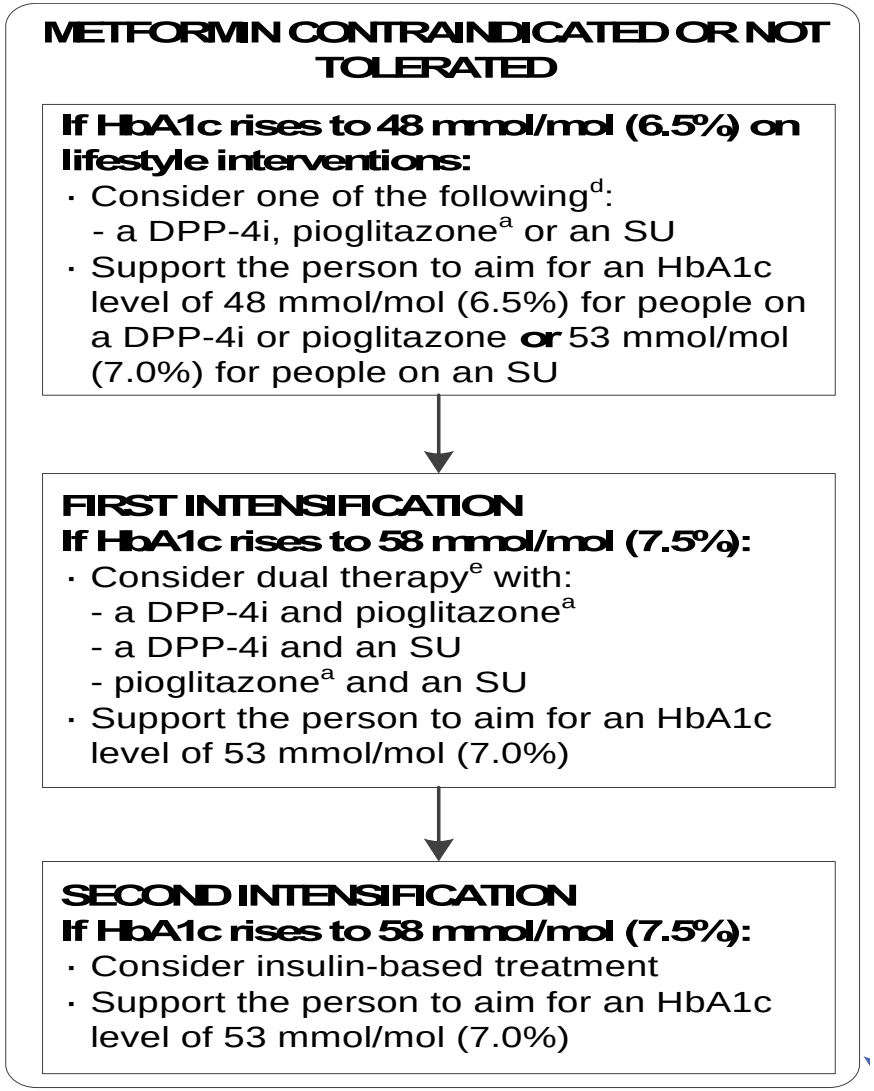
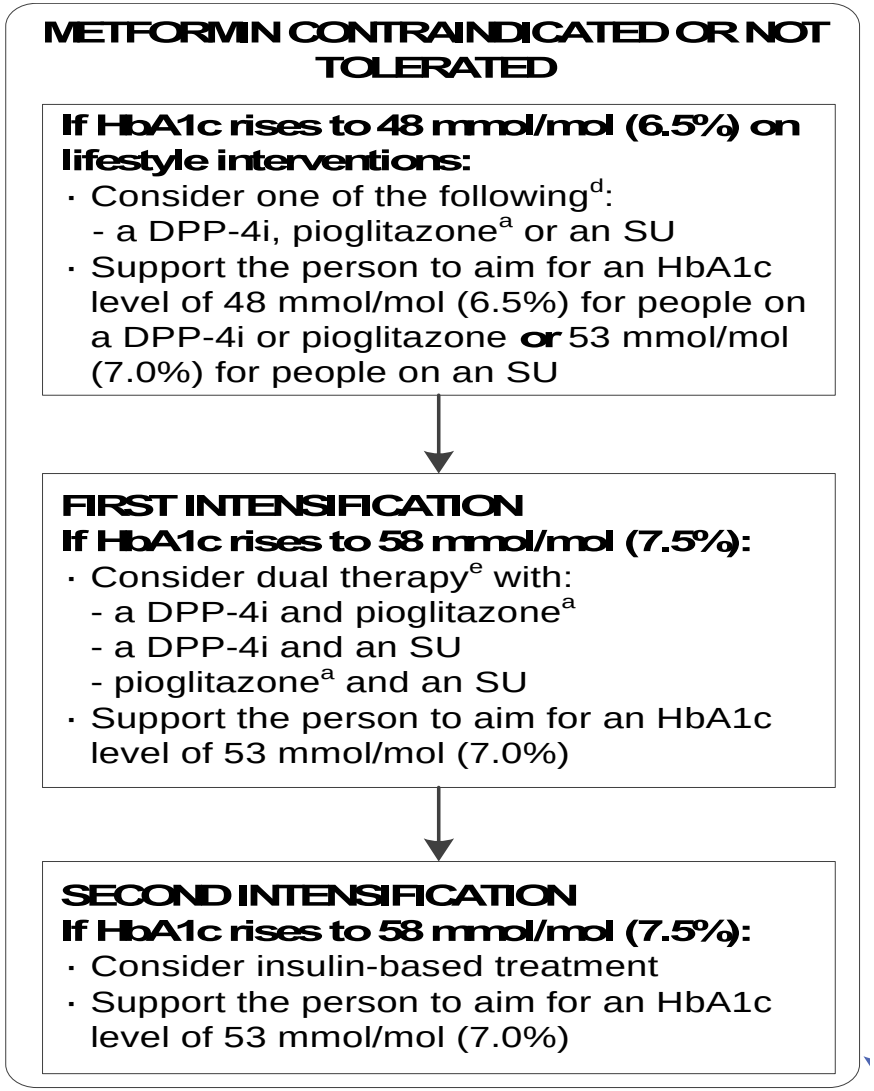
OBJECTIVE — This study evaluated the effects of exenatide, a novel incretin mimetic, in hyperglycemic patients with type 2 diabetes unable to achieve glycemic control with metformin-sulfonylurea combination therapy.

In most individuals with type 2 diabetes, hyperglycemia results from a failure of β-cell insulin secretory capacity to adequately compensate for insulin resistance in peripheral tissues (1,2). Results from the U.K. Prospective Diabetes Study indicate that β-cell failure is a progressive defect even in the setting of effective glucose-lowering therapy with diet, metformin, sulfonylureas, or insulin (3–

For the 10% who cannot take metformin



For the 10% who cannot take metformin



Which?

What about an SGLT2 i?

What about a GLP-1 RA?

Insulin-based treatment

Insulin-based treatment

- When starting insulin, use a structured programme and continue metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies[f].
- Offer NPH insulin once or twice daily according to need.
- Consider starting both NPH and short-acting insulin either separately or as pre-mixed (biphasic) human insulin (particularly if HbA1c is 75 mmol/mol (9.0%) or higher).
- Consider, as an alternative to NPH insulin, using insulin detemir or glargine[g] if the person: needs assistance to inject insulin, lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes **or** would otherwise need twice-daily NPH insulin in combination with oral blood glucose lowering drugs.
- Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if: the person prefers injecting insulin immediately before a meal, hypoglycaemia is a problem **or** blood glucose levels rise markedly after meals.
- Only offer a GLP-1 mimetic[c] in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team[h].
- Monitor people on insulin for the need to change the regimen.
- [illegible]

Insulin-based treatment

Insulin-based treatment

- When starting insulin, use a structured programme and continue metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies[f].
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- Only offer a GLP-1 mimetic[c] in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team[h].
- Monitor people on insulin for the need to change the regimen.
- [illegible]

Agree

Agree

The small print

Abbreviations: DPP-4i Dipeptidyl peptidase-4 inhibitor, GLP-1 Glucagon-like peptide-1, SGLT-2i Sodium–glucose cotransporter 2 inhibitors, SU Sulfonylurea. Recommendations that cover DPP-4 inhibitors, GLP 1 mimetics and sulfonylureas refer to these groups of drugs at a class level.

a. When prescribing pioglitazone, exercise particular caution if the person is at high risk of the adverse effects of the drug. Pioglitazone is associated with an increased risk of heart failure, bladder cancer and bone fracture. Known risk factors for these conditions, including increased age, should be carefully evaluated before treatment: see the manufacturers' summaries of product characteristics for details. Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2011) advises that 'prescribers should review the safety and efficacy of pioglitazone in individuals after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated'.

b. Treatment with combinations of drugs including sodium–glucose cotransporter 2 inhibitors may be appropriate for some people at first and second intensification; see NICE technology appraisal guidance 288, 315 and 336 on dapagliflozin, canagliflozin and empagliflozin respectively. All three SGLT-2 inhibitors are recommended as options in dual therapy regimens with metformin under certain conditions. All three are also recommended as options in combination with insulin. At the time of publication, only canaglifozin and empagliflozin are recommended as options in triple therapy regimens. The role of dapagliflozin in triple therapy will be reassessed by NICE in a partial update of TA288. Serious and life-threatening cases of diabetic ketoacidosis have been reported in people taking SGLT-2 inhibitors (canagliflozin, dapagliflozin or empagliflozin) or shortly after stopping the SGLT-2 inhibitor. MHRA guidance (2015) advises testing for raised ketones in people with symptoms of diabetic ketoacidosis, even if plasma glucose levels are near normal.

c. Only continue GLP-1 mimetic therapy if the person has a beneficial metabolic response (a reduction of HbA1c by at least 11 mmol/mol [1.0%] **and** a weight loss of at least 3% of initial body weight in 6 months).

d. Be aware that, if metformin is contraindicated or not tolerated, repaglinide is both clinically effective and cost effective in adults with type 2 diabetes. However, discuss with any person for whom repaglinide is being considered, that there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification.

e. Be aware that the drugs in dual therapy should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug.

f. MHRA guidance (2011) notes that cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. It advises that if the combination is used, people should be observed for signs and symptoms of heart failure, weight gain, and oedema. Pioglitazone should be discontinued if any deterioration in cardiac status occurs.

g. The recommendations in this guideline also apply to any current and future biosimilar product(s) of insulin glargine that have an appropriate Marketing Authorisation that allows the use of the biosimilar(s) in the same indication.

h. A consultant-led multidisciplinary team may include a wide range of staff based in primary, secondary and community care.

The small print c

- “Only continue GLP-1 mimetic therapy if the person has a beneficial metabolic response (a reduction of HbA1c by at least 11 mmol/mol (1%) **and** a weight loss of at least 3% of initial body weight in 6 months”

➢ So what about the results of the ABCD audits?

The small print d

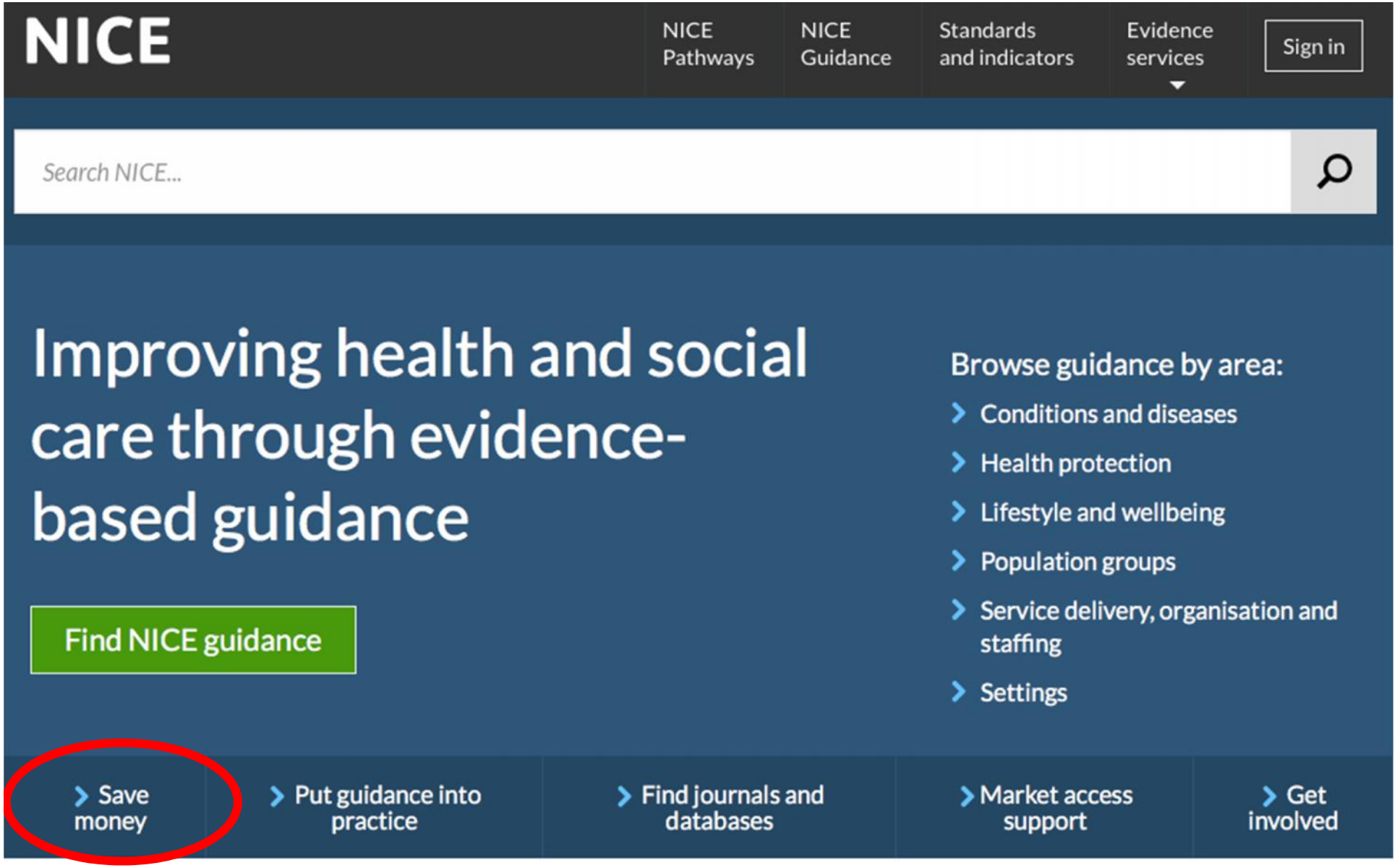
- “Be aware that, if metformin is contraindicated or not tolerated, repaglinide is both clinically effective and cost effective in adults with type 2 diabetes. However, discuss with any person for whom repaglinide is being considered that there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification ”

The small print h

- “A consultant-led multidisciplinary team may include a wide range of staff based in primary, secondary and community care”

Problems with the algorithm and guideline

- Too much text and not enough graphics
- No clarity about different drug classes
- SGLT2 inhibitors not fully covered
- Positioning of GLP-1 RAs late plus GLP-1RAs are described at “class level”
- No acknowledgment of cardiovascular outcomes results with empagliflozin and liraglutide


NICE
NICE Pathways
NICE Guidance
Standards and indicators
Evidence services
Sign in
Search NICE...
Improving health and social care through evidence-based guidance
Find NICE guidance
Browse guidance by area:
Conditions and diseases
Health protection
Lifestyle and wellbeing
Population groups
Service delivery, organisation and staffing
Settings
Save money
Put guidance into practice
Find journals and databases
Market access support
Get involved

Appendix B Scope for update

4.3.2 Areas from the original guidelines that will be updated by an evidence review

1. Pharmacological management of blood glucose levels. The following blood glucose-lowering therapies will be examined as part of treatment strategies involving monotherapy, dual therapy and triple therapy [a]:

- DPP-4 inhibitors:
  - sitagliptin, vildagliptin, linagliptin and saxagliptin
- glucagon-like peptide-1 (GLP-1) receptor agonists:
  - exenatide (conventional formula and prolonged release), lixisenatide and liraglutide
- thiazolidinediones (peroxisome proliferator-activated receptor gamma [PPAR-γ] agonists):
  - pioglitazone
- sulfonylureas
- metformin
- insulin
- acarbose
- meglitinides.

Appendix B Scope for update

4.3.4 Areas from the original guidelines that will not be updated by an evidence review

1. Patient education (including structured education).
2. Dietary advice.
3. Management of depression.
4. Screening for diabetic retinopathy.
5. Pharmacological management of blood glucose levels:

- sodium glucose cotransporter 2 (SGLT-2) inhibitors. It is intended that these drugs will be covered by NICE technology appraisals guidance. The clinical guideline intends to use these drugs as comparators but will not make new recommendations on their use
- rosiglitazone (original recommendations removed following European Medicines Agency [EMA] safety warning, September 2010)
- alogliptin (full license not anticipated to be in time for inclusion within the guideline)

6. Blood pressure control (including target values and pharmacological management).

Research recommendations

2.4 Long-term outcomes associated with blood glucose lowering agents

In adults with type 2 diabetes, what are the long-term effects of blood glucose lowering therapies such as dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium–glucose cotransporter-2 (SGLT-2) inhibitors and meglitinides?

Why this is important

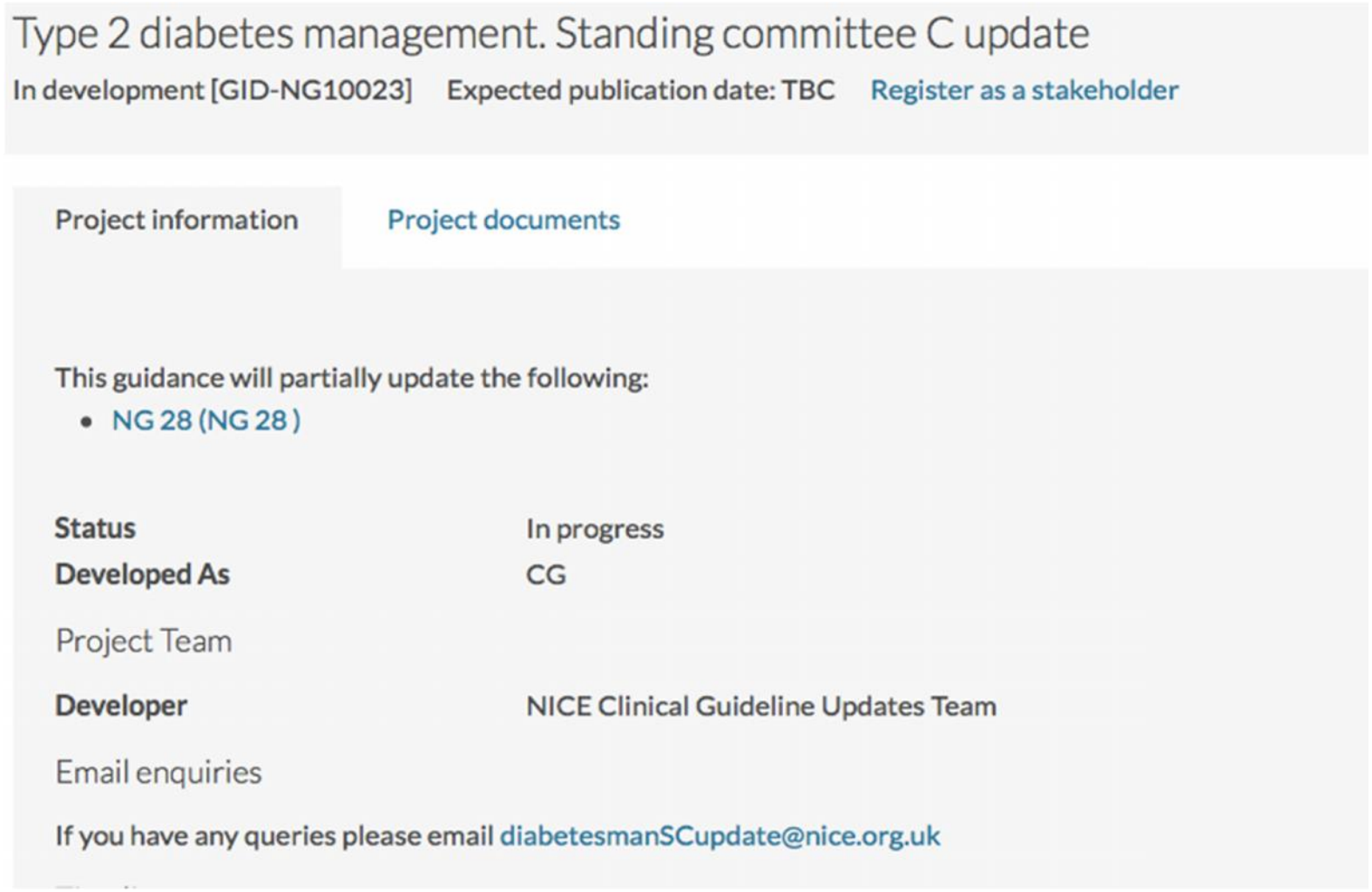
There is limited evidence in relation to the long-term effects (at least 5 years) of blood glucose lowering therapies, particularly newer agents in terms of efficacy and adverse events (for example, cardiovascular outcomes). Randomised controlled trials and prospective longitudinal studies are needed to better understand the long-term efficacy and safety issues surrounding these medicines.

What next for NICE and T2DM?

December 2015: This guidance updates and replaces NICE guideline CG87 (published May 2009). It also updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248.

It has not been possible to update all recommendations in this update of the guideline. Areas for review and update were identified and prioritised through the scoping process and stakeholder feedback. Areas that have not been reviewed in this update may be addressed in 2 years' time when NICE next considers updating this guideline. NICE is currently considering setting up a standing update committee for diabetes, which would enable more rapid update of discrete areas of the diabetes guidelines, as and when new and relevant evidence is published.

What next for NICE and T2DM?



Type 2 diabetes management. Standing committee C update

In development [GID-NG10023] Expected publication date: TBC Register as a stakeholder

Project information | Project documents

This guidance will partially update the following:

- NG 28 (NG 28)

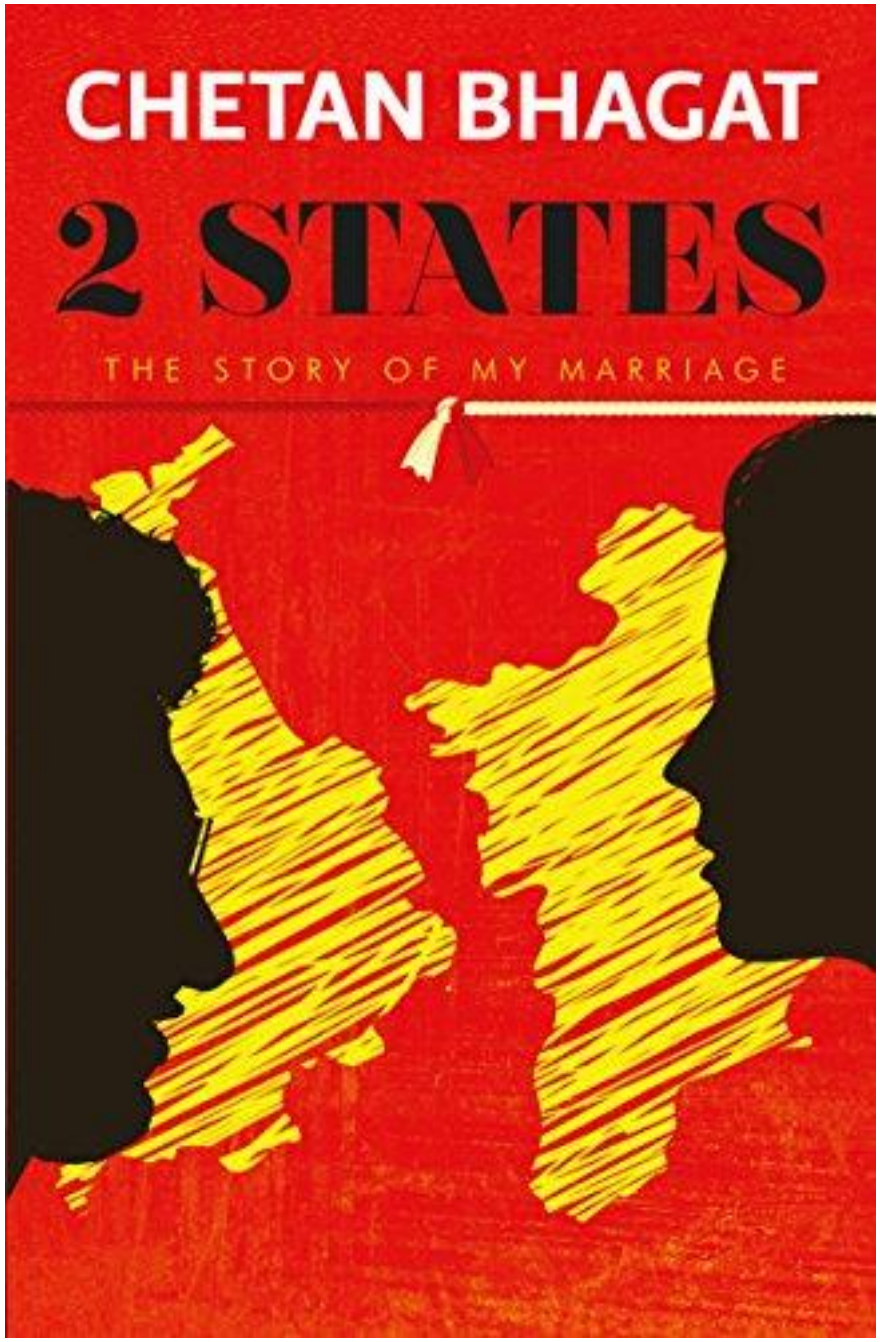
Status	In progress
Developed As	CG

Project Team

Developer	NICE Clinical Guideline Updates Team

Email enquiries

If you have any queries please email diabetesmanSCupdate@nice.org.uk


CHETAN BHAGAT
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THE STORY OF MY MARRIAGE

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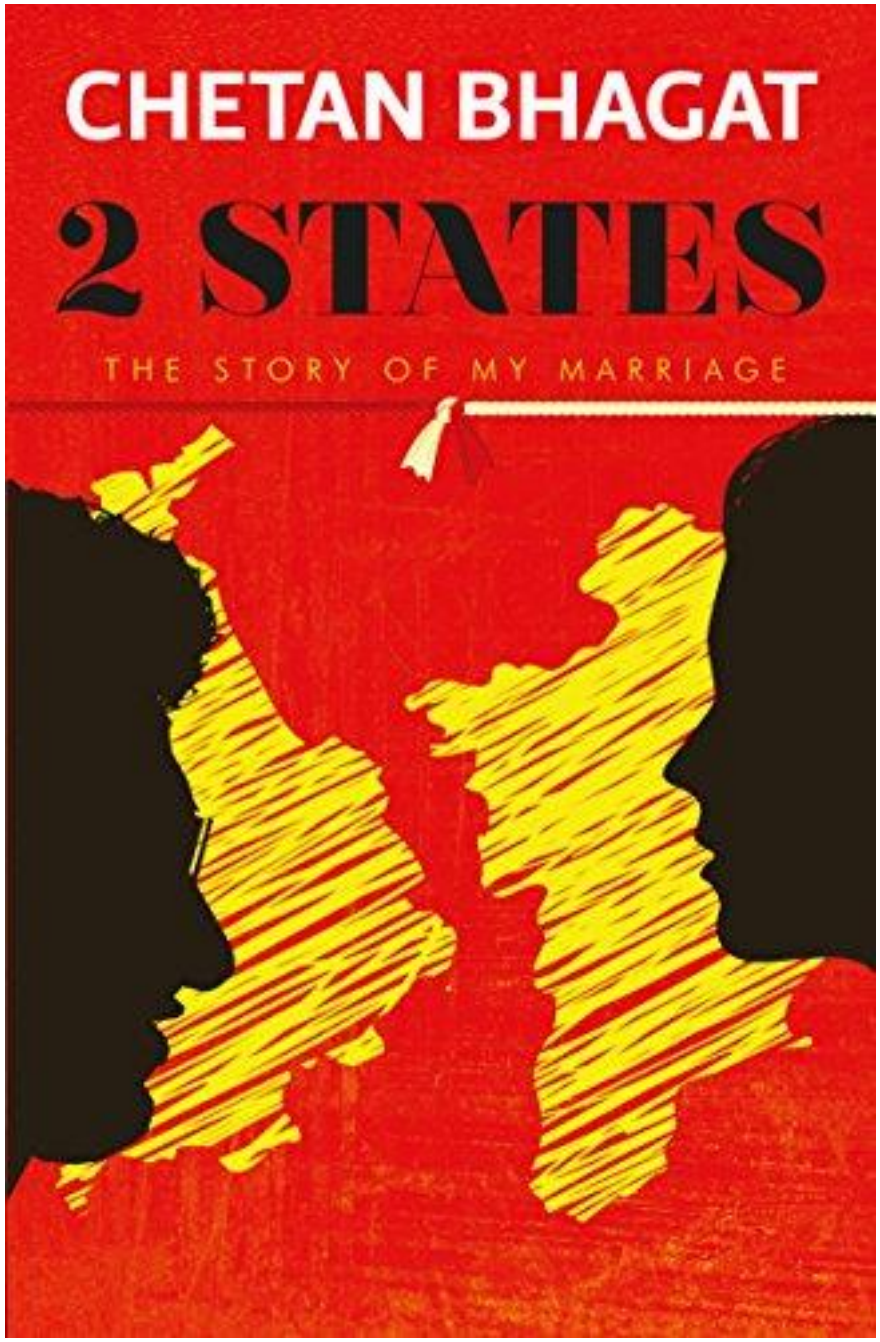

NHS
National Institute for
Health and Clinical Excellence

This house believes that the current NICE guidelines are out of date, lack patient focus, and are not fit for purpose

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